

**● PRINTER RUSH ●**  
**(PTO ASSISTANCE)**

Application : <u>09/627,600</u>	Examiner : <u>Liu</u>	GAU : <u>1653</u>
From: <u>DP</u>	Location: <u>IDC</u> FMF FDC	Date: <u>12/20/05</u>

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<input type="checkbox"/> 1449	_____	<input type="checkbox"/> Continuing Data
<input type="checkbox"/> IDS	_____	<input type="checkbox"/> Foreign Priority
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<input type="checkbox"/> IIFW	_____	<input type="checkbox"/> Fees
<input type="checkbox"/> SRFW	_____	<input type="checkbox"/> Other
<input type="checkbox"/> DRW	_____	
<input type="checkbox"/> OATH	_____	
<input type="checkbox"/> 312	_____	
<input checked="" type="checkbox"/> SPEC	<u>7/28/2000</u>	

[RUSH] MESSAGE: Specification: page 11 line # 19 - U.S. Patent  
Application No \_\_\_\_\_, filed on \_\_\_\_\_ is missing. please  
provide.

Thank you.

[XRUSH] RESPONSE: Done

INITIALS: DP

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REV 10/04

Certain therapeutic drugs contain primary amines and are among the preferred agents.

These include the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the pteridine family of drugs, diynenes, the podophyllotoxins, and the taxanes. Particular useful members of these classes include, for example, doxorubicin, daunorubicin, carminomycin, idarubicin, epirubicin, aminopterin, methotrexate, methopterin, mitomycin C porfiromycin, 5-fluorouracil, cytosine arabinoside, etoposide, melphalan, vincristine, vinblastine, vindesine, 6-mercaptopurine, and the like.

Other therapeutic drugs are required to have primary amines introduced by chemical or biochemical synthesis, for example sesquiterpene-lactones such as thapsigargin, and thapsigargin and many others known to those skilled in the art. The thapsigargin is a group of natural products isolated from species of the umbelliferous genus *Thapsia*. The term thapsigargin has been defined by Christensen, *et al.*, *Prog. Chem. Nat. Prod.*, 71 (1997) 130-165. These derivatives contain a means of linking the therapeutic drug to carrier moieties, including peptides and antibodies. The peptides and antibodies can include those which specifically interact with antigens including hK2. The interactions can involve cleavage of the peptide to release the therapeutic analogs of sesquiterpene- $\gamma$ -lactones. Particular therapeutic analogs of sesquiterpene- $\gamma$ -lactones, such as thapsigargin, are disclosed in United States Patent Application No. 09/588,822, filed June 7, 2000, entitled "Tissue Specific Prodrug," and United States Patent Application No. 09/588,921, filed June 7, 2000, ~~on even date herewith~~, entitled "Tissue Specific Prodrug," both of which are incorporated herein in their entireties.

For example, thapsigargin with alkanoyl, alkenoyl, and arenoyl groups at carbon 8 or carbon 2, can be employed in the practice of the invention disclosed herein. Groups such as  $\text{CO}-(\text{CH}=\text{CH})_{n1}-(\text{CH}_2)_{n2}-\text{Ar}-\text{NH}_2$ ,  $\text{CO}-(\text{CH}_2)_{n2}-(\text{CH}=\text{CH})_{n1}-\text{Ar}-\text{NH}_2$ ,  $\text{CO}-(\text{CH}_2)_{n2}-(\text{CH}=\text{CH})_{n1}-\text{CO}-\text{NH}-\text{Ar}-\text{NH}_2$  and  $\text{CO}-(\text{CH}=\text{CH})_{n1}-(\text{CH}_2)_{n2}-\text{CO}-\text{NH}-\text{Ar}-\text{NH}_2$  and substituted variations thereof can be used as carbon 8 substituents, where  $n1$  and  $n2$  are from 0 to 5, and Ar is any substituted or unsubstituted aryl group. Substituents which may be present on Ar include short and medium chain alkyl, alkanoxy, aryl, aryloxy, and alkenoxy groups, nitro, halo, and primary secondary or tertiary amino groups, as well as such groups connected to Ar by ester or amide linkages.

In other embodiments of thapsigargin analogs, these substituent groups are represented by unsubstituted, or alkyl-, aryl-, halo-, alkoxy-, alkenyl-, amido-, or amino-substituted  $\text{CO}-(\text{CH}_2)_{n3}-$